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REMARKS/ARGUMENTS

insert stmt re claims-pending and under examination

Applicants have amended the specification to update the status of the applications from which the instant application claims priority.

Double Patenting

Claims 42-44, 48, and 51-54 are allegedly unpatentable over the claims of US 6,284,221 in light of Vigo-Pelfrey et al and Sukuki et al. because it would have been obvious to modify the assay of US 6, 284,221 by measuring the species of soluble Aβ(x≥41) by means of the assay of Suzuki et al. because Viego-Pelfrey et al. teach that Aβ(1-42) is a soluble species of Aβ present in fluid samples of disease individuals. It is noted that the double patent rejection of claims 42-48 and 50 as being obviousness over US 6,284,221 in view of Viego Pelfrey et al. alone has been withdrawn and been replaced with a new argument.

1. A method for identifying .beta.-amyloid (.beta.AP) production inhibitors, said method comprising: administering a test compound to a mammalian host; and determining whether the test compound affects the amount of a soluble .beta.AP peptide present in a body fluid sample; wherein reduction in the amount is indicative of inhibition of production of the .beta.AP peptide.

2. A method as in claim 1, wherein the mammalian host is selected from the group consisting of monkeys, dogs, rabbits, guinea pigs, rats, and mice.

3. A method as in claim 2, wherein the mammalian host is a mouse.

4. A method as in claim 3, wherein the mouse is a transgenic mouse comprising DNA encoding an amyloid precursor protein variant.

5. A method as in claim 1, wherein the body fluid is selected from the group consisting of blood, CSF, urine, and peritoneal fluid.

6. A method as in claim 1, wherein the test compound is administered orally, topically, intramuscularly, intravenously, subcutaneously intraventricularly, or intraperitoneally.

7. A method as in claim 1, wherein the effect of the test compound is determined by measuring a baseline amount of soluble .beta.AP peptide in a body fluid sample prior to administering the test compound and remeasuring the amount of soluble .beta.AP in the body fluid after a predetermined time period has elapsed.

8. A method as in claim 1, wherein the soluble .beta.AP peptide is intact .beta.AP.

9. A method as in claim 1, wherein the soluble .beta.AP peptide is an approximately 3 kD fragment of .beta.AP.

The diagnostic method disclosed in U.S. 6,284,221 (the '221 patent) relies on the discovery that the presence of the Aÿ-related condition will generally be associated with elevated levels of Aÿ in a patient's body fluid when compared to those values in normal individuals, *i.e.*, individuals not suffering from Alzheimer's disease or any other Aÿ-related condition. The diagnostic methods of the '221 patent and the present invention rely on different diagnostic indicators. The method of the '221 patent correlates high levels of soluble Aÿ with Alzheimer's disease, while the present invention correlates Aÿ (x- 41) in amounts that are in the very low end of the normal range with Alzheimer's disease. The disclosure of the '221 patent does not suggest that one of skill in the art would expect to find levels Aÿ (x- 41) in amounts which are in the very low end of the normal range present in the CSF of non-Alzheimer's individuals.

Suzuki et al. discuss the use *of the monoclonal 226 antibody, which is raised against Aÿ-28, to isolate and characterize of multiple complex forms of Aÿ from CSF. Aÿ species containing 27, 28, 30, 35, 40, 42, and 43 amino acids were identified using laser desorption mass spectrometry.* Suzuki et al. discuss neither a screening method nor a method to distinguish

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between Aβ(x≥41)and Aβ(x≤40). Suzuki et al. do not appreciate the discovery which the present invention relies on, at least in part, *i.e.*, that the cerebrospinal fluid (CSF) of individuals suffering from Alzheimer's disease generally contains Aβ (x≥41) in amounts which are in the very low end of the normal range present in the CSF of non-Alzheimer's individuals. The Aβ species identified by Suzuki et al. do not suggest that one of skill in the art would expect to find levels Aβ (x≥41) in amounts which are in the very low end of the normal range present in the CSF of non-Alzheimer's individuals.

The disclosure of Suzuki et al. would not prompt the skilled person to modify or adapt the '221 patent to arrive at the presently claimed invention. The present invention results at least in part from the discovery that the cerebrospinal fluid (CSF) of individuals suffering from Alzheimer's disease generally contains Aÿ (x- 41) in amounts which are in the very low end of the normal range present in the CSF of non-Alzheimer's individuals. This discovery is new and surprising because elevated levels of Aÿ in body fluids are associated with Alzheimer's disease, and because the bulk of Aÿ deposits in the brain tissue of persons suffering from Alzheimer's disease is Aÿ42. Without the knowledge of the discovery of the present invention, a skilled person would not have modified or adapted the diagnostic method disclosed in the '221 patent with the Aÿ species identified by Vigo-Pelfrey et al.

The Office Action mailed July 5, 2000 asserts that "Suzuki et al. teach a sandwich immunoabsorbent assay which measure Aβ(1-42) in a fluid enzyme-linked immunoassays to detect the long and short forms of Aÿ are useful to detect inhibitors and assembly of reagents and instructions for use into a kit format because such kits formats are conventional in the art. (See the Office Action mailed July 5, 2000, paragraph 11).

Claims 40 and 42, and the claims depending therefrom, require instructions to screen for compounds that differentially alter production of the longer forms of Aÿ (x41) compared with the shorter forms of Aÿ (x40) or with total Aÿ.

Suzuki et al. contains no discussion of screening compounds for any purpose. Thus, Suzuki et al. certainly fail to (1) provide some suggestion or motivation to modify the

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reference; (2) a reasonable expectation of success; and, (3) teach correlating a statistically significant difference between the first degree of alteration and the second degree of alteration with the ability of the compound to differentially alter the amount of at least one A (x-41) peptide produced by a cell compared with the amount of either total A or at least one A (x-40) peptide produced by the cell..

In light of the foregoing remarks, Applicants respectfully request that the rejection of claims 40-51 under 35 U.S.C. § 103 (a) for allegedly being obvious over Suzuki et al.

C. Rejection of claims 40-51 under 35 U.S.C. § 103 (a) for allegedly being obvious over Odaka et al. (Suzuki et al.)

Claims 40-51 were rejected under 35 U.S.C. § 103 (a) for allegedly being unpatentable over Suzuki et al. (Biochemistry, 34:10272-10278, 1995). The rejection is respectfully traversed. Applicants note that Odaka et al. (Biochemistry, 34:10272-10278, 1995) is the same reference as Suzuki et al. (Biochemistry, 34:10272-10278, 1995).

As already noted above, obviousness under § 103 requires that the cited prior art references provide: (1) some suggestion or motivation to modify the reference; (2) a reasonable expectation of success; and, (3) all claim limitations must be taught or suggested.

The Office Action mailed July 5, 2000 asserts that "Suzuki et al. teach that enzyme-linked immunoassays to detect the long and short forms of Aβ are useful to detect inhibitors and assembly of reagents and instructions for use into a kit format because such kits formats are conventional in the art. (See the Office Action mailed July 5, 2000, paragraph 12).

For the reasons stated above in section A (rejection of claims 21-51 and 59-61 under 35 U.S.C. § 103 (a) for allegedly being obvious over Odaka et al. in view of Haass, Iwatsubo et al., and Wadsworth et al.), Odaka et al. does not (1) provide a suggestion or motivation to modify the references; (2) a reasonable expectation of success; and, (3) teach all limitations of the claims. Thus, Applicants respectfully request that the rejection of claims 40-51 under 35 U.S.C. § 103 (a) for allegedly being obvious over Odaka et al. (Suzuki et al.).

35 U.S.C. § 112, First Paragraph

Enablement

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Claims 45 and 46 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. Without conceding that the Examiner's rejection is warranted, claim 45 has been amended to a recite a "rodent animal model" and claim 46 has been canceled.

Written Description

Claims 48 and 52-54 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. **need argument**

Claims 48 and 51-54 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Claim 53 has been canceled and claims 48, 51, 52, and 54 have been amended for greater clarity in accordance with the teaching of the specification. When it is said that an antibody or fragment thereof binds to Aβ(x-42), what is meant is that it binds to Aβ(x-42) and does not cross-react with Aβ(x$\leq$42), but may bind to Aβ(x-41) or Aβ(x-41). Based on the foregoing, Applicants respectfully request the rejection be withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 43-46 and 48 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention. Claims 43-46 and 48 as presently presented do not contain two recitations of the work "claim." Claims 43, 45, and 48 depend from claim 42. Claim 44 depends from claim 43. Claim 46 depends from claim 45. Applicant do not intend for of the claims to be multiple dependent claims.

Claim 45 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite from the use of the acronym APP. The claim has been amended to recite "amyloid precursor protein (APP)."

All amendments are for the purposes of expediting prosecution and should not be construed as an acquiescence in any ground of rejection.

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If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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